04-C-0168: Pediatric Phase I Trial of LMB-2 for Refractory CD25-Positive Leukemias and Lymphomas

This is a phase I trial of the recombinant immunotoxin anti-Tac(Fv)-PE38 (LMB-2) in pediatric patients with refractory CD25 (IL2Ra, Tac) expressinghematopoietic malignancies. The scientific basis for this study is that patients with these malignancies have cells that express high levels of the Tac antigen on their cell surface, whereas the normal cells of the patients, including resting T-cells, do not. Therapeutic efficacy was observed in a phase I trial of LMB-2 in adults with CD25 expressing hematopoietic malignancies. In this trial, LMB-2 will be administered to children and adolescents with CD25-positive hematopoietic malignancies that have been refractory to standard therapy. Patients will be followed closely for evidence of clinical or laboratory toxicity. Clinical response will be evaluated using routine hematologic and clinical evaluation and, when appropriate, by monitoring the phenotype of circulating malignant cells, bone marrow, or tumor tissue. LMB-2 pharmacokinetics and levels of anti-immunotoxin antibodies will also be monitored. It is hoped that this phase I trial will lead to the development of a new, specific therapy for CD25 positive hematopoietic malignancies of childhood and adolescence.

Eligibility Criteria

- Age: Patient age: > 6 months and < 18 years.
- Histologic diagnosis: All patients must have a histologically confirmed diagnosis of one of the following:
  - Non-Hodgkin's lymphoma (NHL) including lymphoblastic lymphoma, Burkitt's lymphoma, large cell lymphoma, adult T-cell leukemia/lymphoma (ATL), cutaneous T-cell lymphoma (CTCL), peripheral T-cell lymphoma (PTCL)
  - Hodgkin's disease (HD)
  - Acute myelogenous leukemia (AML)
  - Chronic myelogenous leukemia (CML)
  - Acute lymphoblastic leukemia (ALL)
  - Acute hybrid leukemia (including mixed lineage, biphenotypic, and undifferentiated)
- CD25 expression: Patients must have evidence of CD25 positivity by at least one of the following criteria:
  - 15% of malignant cells from a site react with anti-CD25 by immunohistochemistry
  - 30% of malignant cells from a site are CD25+ by FACS analysis
- Stage of Disease and Prior Therapy:
  - Patients must have measurable or evaluable disease.
  - Patients must have relapsed or refractory disease after at least one standard chemotherapy and one salvage regimen. Patients with acute leukemia must have >25% blasts in the bone marrow (i.e., M3 marrow classification).
  - In the view of the PI and the primary oncologist, there must be no available alternative curative therapies and patients must either be ineligible for a hematopoietic stem cell transplant (BMT), have refused BMT, or have disease activity that prohibits the time required to identify a suitable stem cell donor.

- Relapse after prior autologous or allogeneic BMT is allowed. In the event of relapse after prior allogeneic BMT, the patient must be at least day +100 post-transplant.
- Patients must have had their last doses of chemotherapy at least 3 weeks (4 weeks for nitrosoureas) prior to study entry. Patients must have had their last doses of radiation therapy at least 3 weeks prior to study entry with the following exception: Patients who have received or are receiving radiation therapy less than 3 weeks prior to study entry will be not be excluded providing the volume of bone marrow treated is less than 10% and the patient has measurable disease outside the radiation port.
- Patients must have recovered from the acute toxic effects of all prior therapy before entry.
- Patients should be off colony stimulating factors (e.g., G-CSF, GM-CSF, EPO) for at least one week prior to entry.
- Patients receiving corticosteroids are allowed provided there has been no change in dose for at least 2 weeks prior to study entry.
- Patients should be off other investigational agents for at least 30 days prior to entry.

- Performance status:
  - Patients > 12 years of age: ECOG score of 0, 1, or 2
  - Patients < 12 years of age: Lansky scale > 50%
  - Patients who are unable to walk because of paralysis, but who are up in a wheel chair will be considered ambulatory for the purpose of calculating the performance score.
- Hematological function: A patient will not be excluded because of pancytopenia due to disease based on bone marrow analysis. For patients without bone marrow involvement, the absolute neutrophil count (ANC) must be > 1000/mm3 and the platelet count > 50,000/mm3 independent of transfusion.
- Hepatic function: Patients must have adequate liver function defined as total bilirubin within normal limits (< 1.0 mg/dl) and transaminases < 2.5x the upper limit of normal.
- Renal function: Patients must have an age-adjusted normal serum creatinine OR a creatinine clearance ≥ 60 mL/min/1.73 m2.
- Cardiac function: Left ventricular function must be > 90% of lower limit of normal (ECHO LV shortening fraction >28% or MUGA ejection fraction >45%).
- Respiratory function: Oxygen saturation must be > 90%.

Exclusion Criteria

- CNS leukemia or lymphoma as manifested by any of the following:
  - CSF WBC >5/µl and confirmation of CSF blasts.
  - Cranial neuropathies deemed secondary to underlying malignancy.
  - Radiologically detected CNS lymphoma.
  - NB: History of CNS involvement with no current evidence of CNS malignancy <u>is NOT an exclusion.</u>
- Isolated testicular ALL
- Clinically significant unrelated systemic illness that in the judgment of the PI would likely compromise the patient's ability to tolerate therapy.

- Patients whose serum neutralizes > 75% of the activity of 1 μg/mL of LMB-2 in tissue culture, due to either anti-toxin or anti-mouse-IgG antibodies.
- HIV infection
- Active hepatitis B or C infection as defined by seropositive for hepatitis B (HbSAg) or hepatitis C and elevated liver transaminases.
- High risk of inability to comply with protocol treatment.

Pretreatment Evaluation

- CD25 analysis may be performed on peripheral blood, bone marrow, or existing pathologic material from outside institutions after obtaining telephone consent.
- LMB-2 antibodies: A sample will be obtained prior to treatment to rule-out pre-existing neutralizing antibodies to BL22.
- Disease evaluation
    - Histologic diagnosis will be confirmed by NIH Hematopathology review.
    - Documentation of all measurable disease and evaluable abnormalities is required.A sample will be obtained prior to treatment to rule-out pre-existing neutralizing antibodies.
    - Soluble IL2R (Tac antigen) Levels: A sample will be obtained prior to treatment to evaluate whether serum IL2R level can be used as a disease marker.

General Treatment Plan

This is a phase I trial of intravenous LMB-2 administered every other day for three doses. Cycles may be repeated every 28 days. A maximum of 6 total cycles will be administered. Cohorts of 3 to 6 patients will be accrued at each dose level starting at 20 μg/kg days 1, 3 and 5 and increasing to 30 and 40 μg/kg QOD x 3. Patients will be admitted to the inpatient service to receive the study drug for each cycle.

Accrual: This protocol is now open for accrual. Expected accrual will be 20 – 40 patients.